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ORIGINAL ARTICLE

# Intrapleural Tenecteplase Therapy in Treatment of Loculated Parapneumonic Pleural Effusions and Empyema

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**KEYWORDS**

Tenecteplase;
Recombinant tissue plasminogen activators;
Intrapleural fibrinolytics;
Parapneumonic effusion;
Empyema

**Abstract** *Background:* Thoracic empyema (TE) and loculated parapneumonic effusions (CPE) cause considerable morbidity and mortality, with an estimated case-fatality rate of 15%. Intrapleural administration of recombinant tissue plasminogen activators (r-TPA) such as tenecteplase (TNKase) has been recently employed to lyse the fibrinous structures of multiloculated pleural space with reduction of surgical intervention. Yet, there is no enough data concerning intrapleural TNKase in treating patients with CPE or TE. Thus, the objective of this study is to determine the safety and efficacy of TNKase for the treatment of loculated parapneumonic pleural effusions and thoracic empyema after failure of complete drainage using pigtail catheter.

*Patients and methods:* This study was done at Respirology and Interventional Radiology Departments, Farwaniya Hospital, Alrashid Respiratory Centre and Thoracic Surgery Department, Chest Hospital, Ministry of Health, State of Kuwait, between January 2012 and November 2013. 58 patients were admitted with loculated pleural effusions {22 patients (37.9%) with thoracic empyema and 36 patients (62.1%) with complicated parapneumonic effusion}. All patients received intrapleural TNKase after failure of complete drainage of pigtail catheter, which was inserted under chest ultrasound guidance. The evaluation was made according to imaging, laboratory, and clinical status. Adverse effects and hemorrhagic complications were also reported.

*Results:* The overall intrapleural TNKase effectiveness in achieving complete drainage of pleural collections was 49 of 58 cases (84.5%). Intrapleural TNKase was successful in 70% (14 of 20) of patients with TE, and 92.1% (35 of 38) of patients with CPE. The total number of TNKase instillations ranged from 2 to 5 (mean, 3.2). The mean volume of pleural fluid increased significantly after

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TNKase administration ($P < 0.001$). White blood cell count (WBC) and C-reactive protein (CRP) were significantly improved after TNKase instillations (both $P < 0.05$). Complications observed were mild and local bleeding occurred in only 4 patients (6.9%).

*Conclusion:* Intrapleural TNKase is an effective therapy in improving drainage of loculated CPE and TE not drained with pigtail catheters alone and can prevent surgical interventions. Intrapleural TNKase is well tolerated with infrequent adverse events.



## Introduction

Loculated pleural effusions, arising from infection, malignancy, and/or hemothoraces, are common sources of morbidity and mortality for hospitalized patients and remain a common clinical problem with an often protracted course [1]. In Thoracic empyema (TE) and complicated parapneumonic effusions (CPE), white blood cells release permeable factors causing fibrinogen to spill into the pleural space. The fibrinogen is then converted to fibrin that can trap the causative microorganism. This entrapment will prevent the antibiotics from reaching the site of infection [2].

The traditional treatment of pleural drainage via chest tube has been associated with a high failure rate because of the inability to drain loculated areas. These patients traditionally required open surgical decortication [3]. The advent of the minimally invasive video-assisted thoracoscopic surgery (VATS), with low operative morbidity, has become the gold standard for most operative managements [4]. However, due to the invasiveness and complexity of these procedures, there has been a necessity for less invasive methods for cases not responding to standard chest tube drainage.

The pathogenesis of fibrin deposition is thought to be a result of alterations in the balance of procoagulant and fibrinolytic activity; therefore fibrinolytics have been used to promote pleural drainage in these complex pleural processes. Intrapleural administration of streptokinase has been perplexing as a result of the development of antibodies as well as the development of delayed hypersensitivity reaction [5]. Thus, urokinase was introduced to alleviate those issues seen with streptokinase, but there were reported cases of allergic reactions and potential risk of viral transmission [6]. This evolved into the development of alteplase and Tenecteplase (TNKase), which are recombinant tissue plasminogen activators (r-tPAs), produced by recombinant DNA technology, that could be a more appropriate therapeutic agent. This may be secondary to a decreased level of endogenous tPA in pleural fluid or because of inhibition of plasminogen and plasmin by plasminogen activator inhibitors-1 and -2 and other mediators [7]. Tenecteplase is a fibrin specific fibrinolytic. It is different from human tissue plasminogen activator by having three amino acid substitutions. These substitutions increase fibrin binding, increase resistance to plasminogen activator inhibitor-1, and can break up the fibrinous debris, thereby allowing drainage of the fluid [8].

Despite extensive use of intrapleural fibrinolytics in recent years in the treatment of complicated pleural effusions to lyse loculations and promote resolution [9–11], little is known about complications that may arise with the use of this kind of therapy and existing studies, however, are lacking in demonstrating the efficacy of recombinant tissue plasminogen activators particularly intrapleural TNKase administration. Thus, the objective of this study is to determine the safety and efficacy of TNKase for the treatment of loculated parapneumonic pleural effusions and thoracic empyema after failure of complete drainage of pigtail catheter.

## Patients and methods

This study was done at the Respirology and Interventional Radiology Departments, Farwaniya Hospital, Alrashid Respiratory centre and Thoracic Surgery Department, Chest Hospital, Ministry of Health, State of Kuwait, between January 2012 and November 2013. 58 patients were admitted with loculated pleural effusions {22 patients (37.9%) with thoracic empyema and 36 patients (62.1%) with complicated parapneumonic effusion (parapneumonic effusion was defined as an effusion associated with bacterial pneumonia [12]}. All patients received intrapleural TNKase after unfulfilled drainage using a pigtail catheter ($< 70$ mL for the last 24 h) [13], which was inserted under chest ultrasound guidance after exclusion of pigtail catheter blockage, kinking or improper positioning. More than one catheter can be used to help drain off anatomically discrete loculations [14].

All patients were subjected to all of the following: complete history taking, thorough general and local examination, laboratory investigations including CBC, ESR, CRP, and pleural fluid analysis, cultures and cytology, plain chest X-ray and computed tomography scan. Hematological studies including hemoglobin, platelet count, prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT) were taken very early in the morning, every day, before every dose of TNKase instillation [14].

Thoracic empyema (existence of intrapleural frank pus) and complicated parapneumonic effusions (CPE) were defined according to American College of Chest Physicians (ACCP) classification [15] of parapneumonic effusions after pleural fluid analysis (Table 1), using Light's criteria [16] all pleural fluid was exudative in nature (defined as any combination of pleural/serum protein $> 0.5$, pleural lactate dehydrogenase (LDH) level $> 200$ U/L, or pleural/serum LDH level $> 0.6$), with underlying lung infection based on both clinical and radiological evidence of active lung infections, i.e., fever, productive cough with consolidation and loculations with obvious septations confirmed by Chest ultrasound (US) and/or chest computed tomography (CT). Ultrasound detects pleural fluid septations with greater sensitivity than CT, (Table 2) [17]. Patients with other loculated malignant or tuberculous

**Table 1** American College of Chest Physicians classification of parapneumonic effusions.

| Effusion stage | Pleural space anatomy | Pleural fluid bacteriology | Pleural fluid chemistry | Category | Risk of poor outcome | Drainage | Additional fibrinolytic, VATS or surgery required |
|---|---|---|---|---|---|---|---|
| I (uncomplicated parapneumonic) | A0: Minimal, free-flowing effusion (< 10 mm on lateral decubitus) | AND BX: Culture and Gram stain results unknown | AND CX: pH unknown | 1 | Very low | No | No |
| II (uncomplicated parapneumonic) | A1: Small-to-moderate free-flowing effusion (> 10 mm and < 1/2 hemithorax) | AND B0: Negative culture and Gram stain | AND C0: pH ⩾7.2 | 2 | Low | No | No |
| III (complicated parapneumonic) | A2: Large, free-flowing effusion (⩾1/2 hemithorax), loculated effusion or effusion with thickened pleura | OR B1: Positive culture or Gram stain | OR C1: pH < 7.2 | 3 | Moderate | Yes | Yes |
| IV (empyema) | | B2: Pus | | 4 | High | Yes | Yes |

**Table 2** Pleural fluid sonographic appearances.

| Sonographic Appearance | Significance |
|---|---|
| Anechoic (black fluid) | Transudative or exudative effusion |
| Septated (multiple lines within fluid) | Exudative effusion; may suggest possible difficulties inserting chest tube; effusion may drain poorly, although not necessarily |
| Echogenic (echoes, often swirling, within fluid) | Exudative effusion; heavily echogenic fluid suggestive of blood or pus |

effusions were excluded as proved by fluid, microbiology, cytology and/or pleural biopsy.

Once the patient is best positioned for the procedure, chest US was used to determine the optimal needle route to the effusion, without any intervening lung on the planned approach. The movement of the lung should be viewed through a maximal respiratory cycle. A specific pigtail catheter kit (8–10 Fr), (Fig. 1) was used which, has the benefit of a plastic catheter that can be advanced over a metal trocar. Removing the metal trocar immediately as the pleural effusion is entered, while simultaneously advancing the flexible plastic catheter, will have the benefit of decreasing the risk of injury to the lung. The pigtail catheter was placed in the largest loculation and attached to a water-sealed system. Flushing with 15 cc of isotonic normal saline solution 0.9% was done. Drainage was recorded every 8 h (Figs. 2 and 3).

TNKase (Metalyse, Boehringer Ingelheim, Germany) was administered intrapleurally on a daily basis with maximum 5 doses, as a solution of 15 mg TNKase in 100 mL of 0.9% saline solution via three-way stopcock valve connected to the pigtail catheter using a 50 cc syringe. The stopcock valve was subsequently closed for 3 h and the patient was rotated in various positions to disperse the drug. Subsequently, the stopcock was opened to −20 mm Hg suction over an underwater seal device. TNKase was reinstilled, if on repeat chest X-ray, US and/or CT scan, significant persistent pleural effusion was found 24 h after the previous instillation. Pigtail catheter was removed after the total fluid drainage was less than 70 mL in 24 h after subtraction of amount of flushed saline [18,19].

The effectiveness of TNKase was assessed by (1) the percentage of patients achieving complete or near complete drainage of loculated pleural effusion as determined by the volume of fluid drained from the chest tube daily, via serial chest X-ray and chest US and/or CT scan during the five days of intrapleural therapy, (2) the clinical outcome (resolution of symptoms of infection and pleural effusion including, fever and raised white blood count and CRP), (3) hemorrhagic complications associated with catheter drainage [20]. Failure was defined as the (1) failure to resolve loculated effusion (no improvement or worsening in the imaging, manifested by an increase in pleural fluid volume or appearance of new air-fluid levels) or (2) complication necessitating intervention (specifically bleeding that necessitates fluid resuscitation and/or further intervention). Decision to continue TNKase instillation or to proceed to VATS or surgical drainage was taken on the basis of clinical and radiological judgment and signs of sepsis [21].

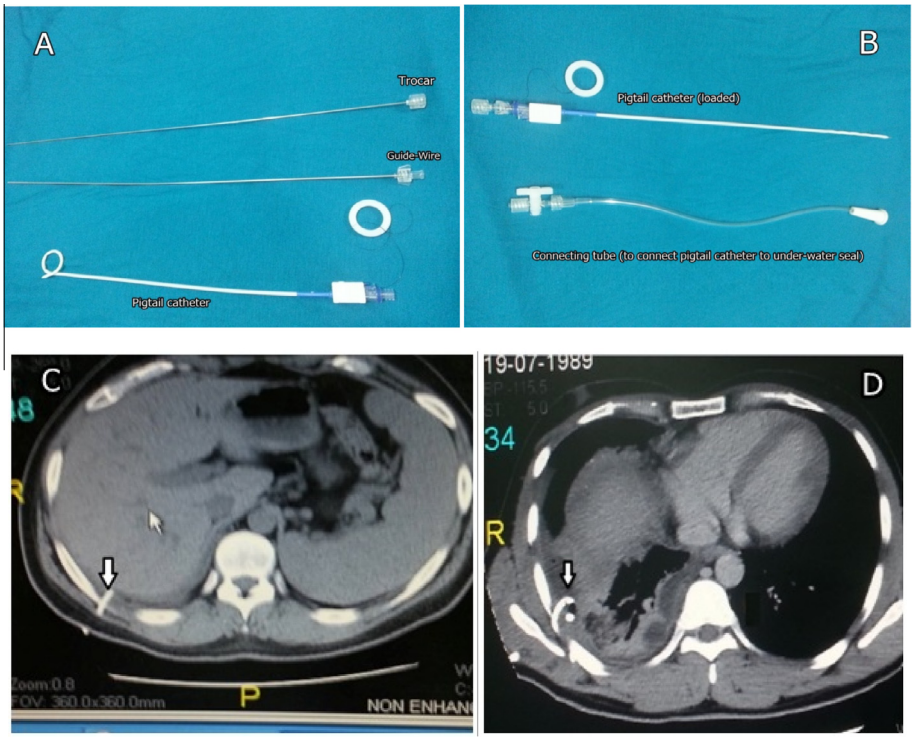


**Figure 1** (A) Pigtail catheter kit components. (B) Pigtail catheter loaded and ready for use. (C) Pigtail inside pleural cavity after intrapleural TNKase instillation with complete drainage. (D) Pigtail inside pleural cavity after TNKase with accepted drainage.

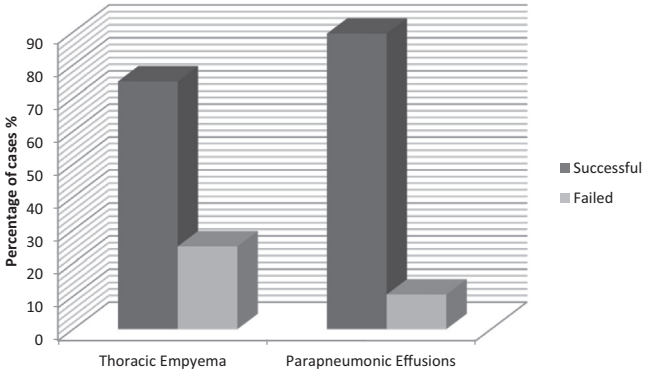


**Figure 2** Successful outcome after TNKase treatment for cases with loculated parapneumonic effusions and thoracic empyema.

## Exclusion criteria

*All patients with one of the following were excluded from the study [22]*

- Other causes of pleural effusion (malignancy, tuberculosis, or hemothorax).
- Active internal bleeding, involving intracranial and retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts.
- History of stroke within 3 months.
- Intracranial neoplasm, arteriovenous malformation, or aneurysm.
- Uncorrectable bleeding diathesis (INR $>1.5$ despite therapy).
- Recent intracranial or intraspinal surgery or head trauma within 14 days.
- Pregnancy (positive pregnancy test).
- Severe uncontrolled hypertension.
- Major thoracic or abdominal surgery within 10 days of admission.
- Known allergy to TNKase.

### *Statistical analysis*

Data were collected using a pre-designed data entry sheet. Analysis was done using statistical software 'SPSS version 10.0' (SPSS Inc, Chicago, IL, USA). Normally distributed variables were summarized as mean with standard deviation and compared using Student's *t*-test. $X^2$ or Fisher exact test was applied to compare the categorical variables. A binary multivariate logistic model was used to identify factors associated with increased risk of bleeding. For all analyses, $P$ value $<0.05$ was considered statistically significant and $P$ value $<0.001$ was considered highly statistically significant.

## Results

This study was done on 58 patients with encysted parapneumonic effusions (38 patients, 65.5%) and thoracic empyema (20 patients, 34.5%). All patients were not drained completely using pigtail catheter therapy and eligible for intrapleural TNKase therapy. Thirty-eight (65.5%) of all patients were male, with total mean age of 49.6 ± 16 years. The overall intrapleural TNKase effectiveness in achieving complete

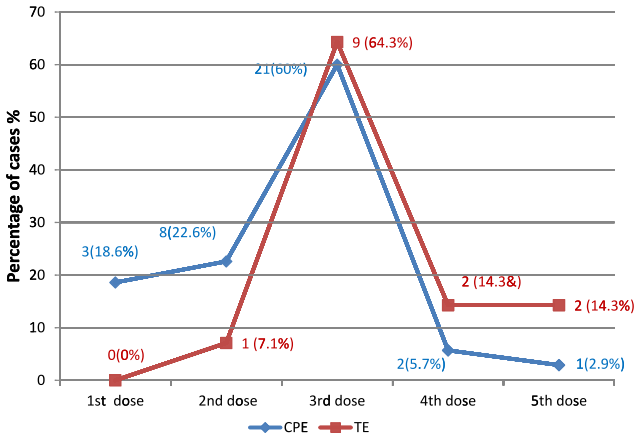


**Figure 3** Successful outcome after TNKase treatment for each dose.

drainage of pleural collections was 49 of 58 cases (84.5%). Intrapleural TNKase was successful in 70% (14 of 20 patients) of patients with thoracic empyema, and 92.1% (35 of 38 patients) of parapneumonic effusions (Fig. 1). Of 49 patients with successful outcome, 8 patients (13.8%) had residual mild pleural processes (< 10% of hemithorax), and accepted as successively treated cases. Only nine patients (15.5%) failed to respond, 8 of them showed thick fibrous peel with lung entrapment, and multiloculated effusion despite full 5 doses of intrapleural TNKase. One case was only marked as failure due to uncontrollable tube bleeding. All failed cases were sent for VATS with debridement and surgical chest tube placement. With follow up, these cases finally had complete resolution of their collections with no mortality.

Tables 3 and 4 show that there were no significant differences between cases responding to intrapleural TNKase fibrinolytic therapy and non-responders regarding clinical or laboratory characteristics or associated comorbidities before starting the therapy, (all $P > 0.05$). In successfully-treated cases with CPE (35 of 38 (92.1%), there was a highly significant difference between the mean duration of fever before and after TNKase instillation (8.6 ± 3.5 days and 2.1 ± 5.0 days respectively) ($P < 0.001$). Other parameters measured also decreased significantly after TNKase instillation, the mean values ± SD of WBC and CRP before TNKase instillation were WBC; 14,322 ± 8625 per $mm^3$ and CRP; 92.48 ± 3.4 mg/dL and WBC; 7106 ± 1526 per $mm^3$ and CRP; 4.22 ± 4.1 mg/dL after TNKase instillation. Also, in successfully-treated cases of with TE (14 of 20 (70%), there was a highly significant difference between the mean duration of fever before and after TNKase instillation (10.0 ± 6.3 days and 3.2 ± 8 days respectively) ($P < 0.001$). Other parameters measured also decreased significantly after TNKase instillation, the mean values ± SD of WBC and CRP before TNKase instillation were WBC; 16,108 ± 4398 per $mm^3$ and CRP; 130.22 ± 10.6 mg/dL and WBC; 8208 ± 3268 per $mm^3$ and CRP; 8.15 ± 2.08 mg/dL after TNKase instillation (all $P < 0.05$, Table 5).

Table 5 shows that there was a highly significant increase in the total mean pleural fluid drainage before and after instillation of TNKase. Before TNKase, the pleural fluid ranged from 120 to 1830 mL with a mean of 623 ± 54 mL. On the other hand, the mean total fluid drained after TNKase instillation was 2350 ± 874 mL (range 1100–4200), ($P < 0.001$). In cases with encysted empyema, the pleural fluid ranged from 150 to 1650 mL with a mean of 420 ± 74 mL and after TNKase instillation, the mean total fluid drained was 2088 ± 502 mL (range 950–3800), ($P < 0.001$). The total number of TNKase instillations ranged from 2 to 5 (mean, 3.2). Fig. 4 shows that the highest mean of pleural drainage was after the 3rd dose in all treated patients.

In responders with loculated CPE, the mean percentage of pleural fluid occupation of the chest X-ray (CXR) was 29 ± 2.3 before TNKase administration. This occupation was highly significantly improved to 5 ± 1.2 after TNKase administration ($P < 0.001$, Table 5). Also, the successfully treated patients with TE, 14 (75%) have significantly improved their CXR after occupation administration (shadow < 10% of hemithorax) after TNKase administration (25.5 ± 4.3 vs 8.0 ± 2.8, $P < 0.05$), Table 4. The loculated collections were demonstrated only in 52 of 58 patients (89.7%) at CT

**Table 3** Baseline demographic and clinical characteristics between successful and failed treated patients before TNKase instillation.

| Total (58 cases) | | CPE 38 (65.5%) | | | TE 20 (34.5%) | | |
|---|---|---|---|---|---|---|---|
| *S* = 49 (84.5%) | *F* = 9 (15.5%) | *S* | *F* | *P* value | *S* | *F* | *P* value |
| No. (%) | | 35 (92.1) | 3 (7.9) | – | 14 (70) | 6 (30) | – |
| Age (mean ± SD) (*T* = 49.6 ± 16) | | 48 ± 40 | 50 ± 18 | > 0.05 | 46 ± 09 | 51 ± 43 | > 0.05 |
| Sex (M/F) (*T* = 38/20) | | 26/9 | 2/1 | > 0.05 | 6/8 | 4/2 | > 0.05 |
| Current smoker | | 9 (25.7) | 1 (33.3) | > 0.05 | 3 (21.4) | 2 (33.3) | > 0.05 |
| Co-morbidity no. (%) | COPD | 3 (8.8) | 0 (0) | > 0.05 | 2 (14.3) | 3 (50) | > 0.05 |
| | CVD | 5 (14.3) | 1 (33.3) | > 0.05 | 2 (14.3) | 1 (16.7) | > 0.05 |
| | DM | 4 (11.4) | 0 (0) | > 0.05 | 3 (21.4) | 3 (50) | > 0.05 |
| | Hepatic diseases | 3 (8.8) | 0 (0) | > 0.05 | 1 (7.1) | 2 (12.5) | > 0.05 |
| | Renal disease | 4 (11.4) | 1 (33.3) | > 0.05 | 2 (14.3) | 3 (50) | > 0.05 |
| Duration of symptoms before inclusion (days), mean ± SD | | 6.6 ± 3.5 | 8.1 ± 5.0 | > 0.05 | 9.1 ± 5.9 | 8 ± 2.1 | > 0.05 |
| Fever > 38.5 °C, *n* (%) | | 28 (80) | 2 (66.7) | > 0.05 | 10 (71.4) | 4 (66.7) | > 0.05 |
| Dyspnea, *n* (%) | | 26 (74.2) | 3 (100) | > 0.05 | 11 (78.8) | 5 (83.3) | > 0.05 |
| Cough, *n* (%) | | 34 (79.1) | 2 (66.7) | > 0.05 | 13 (92.9) | 6 (100) | > 0.05 |
| Sputum production, *n* (%) | | 24 (68.6) | 3 (100) | > 0.05 | 8 (57.1) | 3 (50) | > 0.05 |
| Chest pain, *n* (%) | | 27 (77.1) | 2 (66.7) | > 0.05 | 10 (71.4) | 5 (83.3) | > 0.05 |

**Table 4** Baseline laboratory and radiological characteristics between successful and failed treated patients before TNKase instillation.

| TE 20 (34.5%) | | CPE 38 (65.5%) | | | TE 20 (34.5%) | | |
|---|---|---|---|---|---|---|---|
| *S* = 49 (84.5%) | *F* = 9 (15.5%) | *S* | *F* | *P* value | *S* | *F* | *P* value |
| No. (%) | | 35 (92.1) | 3 (7.9) | – | 14 (70) | 6 (30) | – |
| Pleural Fluid | pH, mean ± SD | 7.0 ± 0.4 | 6.8 ± 0.5 | >0.05 | 6.9 ± 0.1 | 6.8 ± 0.3 | >0.05 |
| | LDH/IU/L (>1000 U), No. (%) | 25 (65.8) | 2 (75) | >0.05 | 14 (100) | 6 (100) | >0.05 |
| | Glucose (<40 mg/dL), No. (%) | 28 (68.4) | 2 (75) | >0.05 | 14 (100) | 6 (100) | >0.05 |
| | WBC (>1000 $mm^3$), No. (%) | 26 (68.4) | 3 (100) | >0.05 | 9 (64.3) | 4 (66.7) | >0.05 |
| US septations, No. (%) total: 37 (63.8) | | 20 (57.1) | 3 (100) | <0.05 | 8 (57.1) | 6 (100) | <0.05 |
| CT loculations, No. (%) total: 52 (89.7%) | | 32 (65.7) | 3 (100) | >0.05 | 12 (85.7) | 5 (83.3) | >0.05 |
| CT pleural thickness mm, mean ± SD | | 6.2 ± 4.3 | 7.8 ± 0.4 | >0.05 | 5.2 ± 1.9 | 5.8 ± 6 | >0.05 |

**Table 5** Indicators of outcome before and after TNKase instillation in successfully-treated patients.

| | Successful cases = 49 (84.5%) | | | | | |
|---|---|---|---|---|---|---|
| | CPE 35 (92.1%) | | | TE 14 (70%) | | |
| | Before | After | *P* value | Before | After | *P* value |
| Duration of fever/days (mean ± SD) | 8.6 ± 3.5 | 2.1 ± 5 | <0.001 | 10.0 ± 6.3 | 420 ± 74 | <0.001 |
| White cell count/$mm^3$ (mean ± SD) | 14,322 ± 8625 | 7106 ± 1526 | <0.05 | 16,108 ± 4398 | 8208 ± 3268 | <0.05 |
| CRP (mg/dL mean ± SD) | 92.48 ± 3.4 | 4.22 ± 4.1 | <0.05 | 130.22 ± 10.6 | 8.15 ± 2.08 | <0.05 |
| Pleural fluid drained amount mL (mean ± SD) | 623 ± 54 | 2350 ± 874 | <0.001 | 420 ± 74 | 2088 ± 502 | <0.001 |
| % area occupied by effusion on CXR (mean ± SD) | 29 ± 2.3 | 5 ± 1.2 | <0.001 | 420 ± 74 | 8 ± 2.8 | <0.05 |
| CT loculations, No. (%) | 32 (65.7) | 5 (14.3) | <0.05 | 420 ± 74 | 3 (21.4) | <0.05 |

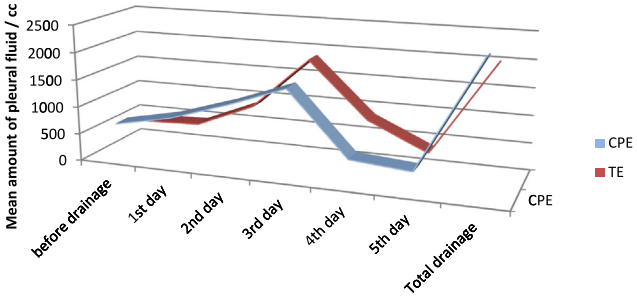


**Figure 4** Mean amounts of pleural fluid drainage before and after TNKase treatment for each dose.

assessment; each of these patients had one to five (mean, 2.2) separate pockets. Six patients had single collections that appeared to layer but drained incompletely after pigtail catheter placement. Table 4 showed that the number of pockets was not a significant predictor of TNKase effectiveness. However, after TNKase administration, there was a significant improvement in the number of loculations in all successful cases ($P < .005$, Table 5). In all cases, the maximum pleural thickness ranged from 1 to 17 mm (mean, 5.4 ± 2.0 mm). In patients successfully treated with CPE, pleural thickness ranged from 1.2 to 12.7 mm with mean 6.2 ± 4.3 mm and for patients in whom TNKase failed, pleural thickness ranged from 1.2 to 14.9 mm with mean 7.8 ± 0.4 with insignificant difference between these two groups ($P > 0.05$). On the other hand, in patients successfully treated with TE, pleural thickness ranged from 1.1 to 14.6 mm with mean 5.2 ± 1.9 mm. For patients in whom TNKase failed, pleural thickness ranged from 1.2 to 17.0 mm with mean 5.8 ± 6. Mean pleural thickness did not differ significantly between these two groups ($P > 0.05$).

There were no complications at the time of catheter placement. Major pleural hemorrhages were occurring with intrapleural TNKase in only four cases (6.9%) {CPE in one (1.7%) and TE in three (5.2%)} and the fibrinolytic therapy was stopped immediately. Hemorrhage occurred 1–2 days after TNKase initiation. Two of bled patients had end-stage renal disease on regular haemodialysis and the other two patients were on infantile dose of aspirin and systemic anticoagulation before TNKase therapy. In these patients, the indicators of hemorrhage were blood in the collection chamber with an associated hemoglobin decrease and worsening of chest radiograph. All hemorrhagic complications required blood transfusion (2–4 units of packed red blood cells). Patients were revaluated after cessation of bleeding. Two of them eventually drained successively via same pigtail catheters and other two patients required VATS. Thus, intrapleural TNKase was successful in clearing a pleural effusion even in the setting of new hemorrhage in 50% (two of four) of patients. All patients who bled survived. No other complications occurred. No systemic hemorrhage was documented in any patient.

Binary analysis did not demonstrate increased bleeding with studied levels of international normalized ratio,

**Table 6** Risk factors for bleeding in all treated patients.

| | | |
|---|---|---|
| INR | | 1.2 ± 0.4 |
| PT | | 15.3 ± 3.8 |
| APTT | | 35.2 ± 9.5 |
| Platelets | | 305.6 ± 152.1 |
| Antithrombotics | None | 41 (70.1%) |
| | Aspirin | 13 (22.4%) |
| | Clopidogrel | 3 (5.2%) |
| | Warfarin | 4 (6.9%) |
| | Dabigatran | 3 (5.2%) |
| | SC heparin | 2 (3.4%) |
| | Heparin infusion | 3 (5.2%) |
| | Enoxaparin | 8 (13.8%) |

Binary analysis did not demonstrate increased bleeding with above all variables ($P > 0.05$).

prothrombin time, partial thromboplastin time and platelets, or those received antithrombotic drugs before TNKase instillation (Table 6). All four hemorrhages occurred in the setting of normal-range of coagulation profile. Of all included patients, four were receiving warfarin, eight were receiving enoxaparin, and five were receiving unfractionated heparin, two were receiving prophylactic SC heparin and 3 patients received heparin infusion. The increased bleeding risk in patients with therapeutic anticoagulation compared with that occurred in patients not receiving any anticoagulation was statistically insignificant ($P < 0.05$). Three of the all patients were receiving clopidogrel, and neither of them bled even though one of them was receiving simultaneous intravenous heparin. Twelve patients were receiving aspirin, six of them were receiving both systemic anticoagulation and aspirin, and two of these six bled.

All patients tolerated well the pigtail drainage procedures and instillation of TNKase. Adverse reactions after TNKase administration were mild and did not affect the TNKase administration, including mild discomfort and dull pain during instillation in 7 patients (12.1%), which was easily managed with analgesic therapy. Mild local hemorrhage occurred in 3 patients (5.2%. Other minor complications include shortness of breath requiring an increase in their oxygen requirement (3 cases, 5.2%) and fever (>38 C) requiring antipyretics (2 cases, 3.4%). No systemic adverse effects of TNKase were recorded, i.e., allergic reaction, hypotension and no significant changes in the coagulation profile of the patients were observed, including the patients who presented pleural hemorrhage after TNKase administration. All patients successfully treated with TNKase had no recurrences and were doing well at the time of discharge.

## Discussion

Loculated empyema and parapneumonic effusions cause considerable morbidity and mortality, with an estimated case-fatality rate of 15% [1]. Many patients require surgical intervention to drain the infected pleural space. Intrapleural administration of fibrinolytic agents has also been widely employed to lyse the fibrinous structures of multiloculated pleural space. Based on early reports of efficacy, the British Thoracic Society (BTS) [23,24] and the ACCP guidelines [15] recommend fibrinolytic drugs as management options.

The current study evaluated the effectiveness and risk factors for complications with the administration of intrapleural Tenecteplase (TNKase). We found that Tenecteplase adjunctive to pigtail catheter drainage significantly improves the outcome of medically treated complicated parapneumonic effusions and thoracic empyema, which led to a reduced need for surgical referral. Our total success rate was 84.5% (49/58 patients). The amount of the pleural fluid drained was significantly improved after TNKase instillation, resulting in a significant improvement of the chest X-ray and CT loculations. Also, we noted a rapid and significant decrease of inflammatory parameters such as WBC and CRP, after intrapleural administration of TNKase. This benefit was achieved without systemic fibrinolysis or systemic hemorrhage.

Several investigators have studied the efficacy and safety of intrapleural t-PA in the treatment of pleural effusion and empyema [21,22]. These researchers report a success outcome defined as improvement of symptoms and X-ray imaging without need for surgical intervention. They used alteplase in place of streptokinase. Alteplase is a direct plasminogen activator, compared with streptokinase, which is indirect. As a result, plasminogen first binds with streptokinase to form an activator complex, which then converts plasminogen to plasmin, whereas alteplase directly converts plasminogen to plasmin. This difference may theoretically lower the levels of plasminogen in the case of streptokinase and make it less efficacious compared with placebo.

Walker et al. [25] first reported the apparent benefits of alteplase in a case with a multi-loculated pleural effusion as an adjunct to chest tube drainage and antibiotics. Subsequently, Skeete et al. [26] instilled t-PA through surgical chest tubes into 42 patients with a variety of pleural conditions, of which 12 were empyemas. They reported accelerated radiological improvement and clinical benefit. Levinson and Pennington [27] used t-PA for 20 patients with largely multiloculated pleural infections; they concluded that t-PA in combination with careful image-guided placement of chest tubes is highly effective in resolving the effusion and curing the infection. Froudarakis et al. [18] found that intrapleural instillation of r-TPA at a dose of 25 mg is a well-tolerated and effective treatment in 95% of adult patients with complicated parapneumonic effusion and empyema. The mean volume of fluid, in their study, increased significantly after r-TPA administration and WBC and CRP were significantly improved after r-TPA instillations. In the study by Gervais et al. [28] 25 patients, with empyemas and complicated parapneumonic effusions, were selected for fibrinolysis with incomplete initial pleural fluid drainage. The overall success rate was 86% based on CT imaging studies obtained before chest tube insertion that demonstrated multiple locules. The authors concluded that rtPA successfully drained effusions that would otherwise have required surgery. Ben-Or et al. [21] have recently used alteplase to treat different complex pleural processes with an overall success rate of 86.4%. They reported that one to two doses was the most successful. Even so, in the MIST II [10] and of Rahman et al. [11] trials the intrapleural t-PA–DNase therapy significantly improved fluid drainage in patients with pleural infection and reduced the frequency of surgical referral and the duration of the hospital stay. However, the treatment with t-PA alone was ineffective. Komissarov et al. [29] reported that plasminogen exhaustion can explain these results and advised to assess intrapleural plasminogen and plasminogen activator

inhibitors-1 prior to intrapleural fibrinolytic injection in order to optimize the outcome.

Regarding the ability of imaging studies to predict the success or failure of fibrinolytic therapy, our study showed that the number of pockets on CT and the percentage of pleural fluid occupation on plain chest X-ray were not a significant predictor of TNKase effectiveness. On the other hand, the presence of US septations was significantly affecting response of intrapleural fibrinolysis. Heterogeneity was present between studies as regards the type of the imaging modality used to predict the pleural fluid resolution. In MIST1 [9] study, radiographic improvement was assessed solely using chest radiographs and not ultrasonography or CT imaging. The appearance of infected collections on chest radiograph depends on the volume and viscosity of pleural fluid, the position of the patient, and the presence of loculations. Limitations of chest radiograph include difficulties in assessing subpulmonic effusions, nondependent loculations, and loculations along the mediastinal pleural reflections. Ultrasound imaging, better than CT imaging, allows characterization of pleural fluid collections with septations; however, CT imaging is better for characterizing loculated effusions in interlobar fissures or adjacent to the mediastinum [30]. In compatible with our results, Gervais et al., [28] reported that CT scan features of number of loculations, degree of pleural thickening (range 1–15 mm), or pleural heterogeneity did not predict ultimate outcome for patients treated with intrapleural recombinant tissue plasminogen activator. Similarly, Levinson and Pennington [27] noted no differences in outcomes between patients with single or multiple loculations treated with intrapleural urokinase or recombinant tissue plasminogen activator. Chen et al. [31] investigated the outcomes of patients who had been diagnosed with empyema and CPE and had received ultrasound-guided small-bore catheter drainage. The appearance of sonographic septation is a useful sign to help predict the outcome of these patients.

The most frightened complication of intrapleural fibrinolytics is bleeding, pleural hemorrhages were occurring in our study after intrapleural TNKase in only four cases (6.9%), which occurred 1–2 days after TNKase initiation. The incidence of bleeding after intrapleural fibrinolytics in the literature ranges between 2% and 15%. This wide range could be explained by differences in patient's selection and type of fibrinolytic used. In the MIST II trial [10], Rahman and Maskell report on five cases of bleeding, including two cases of intrapleural bleeding and one case of haemoptysis that occurred in the tPA and DNase arm (5.76%). Gervais et al., [28] found that systemic anticoagulation does not increase bleeding risk with intrapleural tPA, but therapeutic anticoagulation is associated with a significantly increased risk of pleural hemorrhage. e arm (5.76%). In one recent study of Abu-Daff et al., [14] bleeding occurred in 15 of 227 (6.6%) of their patients. However, three cases required emergency thoracotomy for bleeding, resulting in haemodynamic instability, of which one patient died. Notably, both t-PA and streptokinase were used in this study. This study had some limitations; it is a retrospective study and represented a heterogeneous group of patients with a selection bias. Although we could not identify any specific variable in our study to be statistically associated with bleeding, we did note a trend towards the concomitant use of aspirin as antiplatelet medication with 22.4% of our patients receiving this medication.

## Conclusion

Intrapleural TNKase is an effective therapy in improving drainage of loculated parapneumonic effusions and thoracic empyema not drained with pigtail catheters alone and can prevent surgical interventions. Intrapleural TNKase is well tolerated with infrequent adverse events.

## Conflict of interest

None.

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